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RESEARCH/CLINICAL UPDATE

March 30, 2007

Keyword: Fibrinogen
SECTION: TREATMENTS-INVESTIGATIONAL

ADDITIONAL ROUTING
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Researchers Stop MS-like disease in Mice by Targeting a Blood Protein

A new study funded in part by the National MS Society shows for the first time that blocking a segment of fibrinogen – a protein essential for blood clotting – reduces inflammation and symptoms in mice with an MS-like disease, apparently without interfering with normal blood clotting. Society grantee Katerina Akassoglou, PhD, and postdoctoral fellow Ryan A. Adams, PhD, and colleagues report their findings in *The Journal of Experimental Medicine* (2007 Mar 19;204(3):571-82).

Multiple sclerosis occurs when the immune system attacks the brain and spinal cord, damaging the myelin that insulates and protects nerve fibers. Brain cells known as "microglia" participate in this attack and are activated when the blood brain barrier (BBB) – the lining of cells that should protect the brain from intruders – breaks down. As the BBB breaks down, a blood protein called "fibrinogen" leaks into the brain. In addition to its known role in blood clotting, evidence is growing that fibrinogen also participates in the immune response that goes awry in MS. Dr. Akassoglou's team has uncovered evidence that fibrinogen directly activates microglia, and has developed a method of inhibiting fibrinogen in mice without compromising its clotting capabilities.

The researchers first administered fibrinogen to microglia isolated in lab dishes and found that the protein activated the cells in dramatic fashion. This activation specifically occurred through "Mac-1," a docking site on microglia. Fibrinogen surrounded activated microglia both in mice with the MS-like disease EAE, and in brain tissue from people with MS obtained via autopsy.

Dr. Akassoglou's team genetically engineered mice in which fibrinogen and Mac-1 did not interact, and found that inducing EAE in these mice resulted in less myelin damage and less severe disease. They then administered a small fragment of fibrinogen – which blocks binding of normal fibrinogen to Mac-1 – to mice with an MS-like disease after the first

attack of paralysis. This form of fibrinogen does not block the protein’s interaction with blood platelets, and so would not interfere with clotting. Compared with untreated mice, activation of microglia decreased, myelin damage diminished dramatically, and the treated mice recovered faster and did not experience further relapses.

This study highlights the potential of a novel strategy for inhibiting the immune attack in MS and improving symptoms. Further study is necessary to confirm these findings and to build the information base needed to translate them into a potential treatment strategy in people with MS.

-- Research and Clinical Programs Department